The Oncologist®

Clinical Trial Results

# Phase II Multicenter, Open-Label Study of Oral ENMD-2076 for the Treatment of Patients with Advanced Fibrolamellar Carcinoma

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## Trial Information

- **ClinicalTrials.gov Identifier:** NCT02234986
- **Sponsor:** CASI Pharmaceuticals
- **Principal Investigator:** Ghassan K. Abou-Alfa
- **IRB Approved:** Yes

## Lessons Learned

- The fibrolamellar carcinoma-associated *DNAJB1-PRKACA* gene fusion transcript RNA codes for the catalytic domain of protein kinase A and, thus, overexpression of Aurora kinase A.
- ENMD-2076 showed a favorable toxicity profile.
- The limited results, one patient (3%) with a partial response and 57% of patients with stable disease, do not support further evaluation of ENMD-2076 as single agent.
- Future studies will depend on the simultaneous targeting approach of *DNAJB1-PRKACA* and the critical downstream components.

## Abstract

***Background.*** Fibrolamellar carcinoma (FLC) represents approximately 0.85% of liver cancers. The associated *DNAJB1-PRKACA* gene fusion transcript RNA codes for the catalytic domain of protein kinase A and overexpression of Aurora kinase A (AURKA). ENMD-2076 is a selective anti-AURKA inhibitor.

***Methods.*** Patients aged >12 years with pathologically confirmed incurable FLC, with measurable disease, Eastern Cooperative Oncology Group performance status 0–2 or Lansky 70–100, and adequate organ function were eligible. Patients were prescribed ENMD-2076 based on body surface area. The primary endpoint was overall objective response rate by RECIST v1.1, with a null hypothesis of true response rate of 2% versus one-sided alternative of 15%. Secondary endpoints included 6-month progression-free survival (PFS) rate (Fig. 1), median PFS, time to progression (TTP), and overall survival (OS). Safety was evaluated throughout the study.

***Results.*** Of 35 patients who enrolled and received treatment, 1 (3%) had a partial response (PR) and 20 (57%) had stable disease (SD). Median TTP, PFS, and OS were 5, 3.9, and 19 months, respectively. The most frequently reported drug-related serious adverse event was hypertension in three patients. Three deaths were reported on-study—two due to disease progression and one due to pulmonary embolism not related to ENMD-2076.

***Conclusion.*** The study provided no rationale for further studying ENMD-2076 as a single agent in FLC. ***The Oncologist*** 2020;25:e1837–e1845

## Discussion

Fibrolamellar hepatocellular carcinoma is a very rare liver cancer of adolescents and young adults [1]. It appears that the cancer is driven by a fusion gene, *DNAJB1-PRKACA*, comprising the first exon of *DNAJB1*, the heat-

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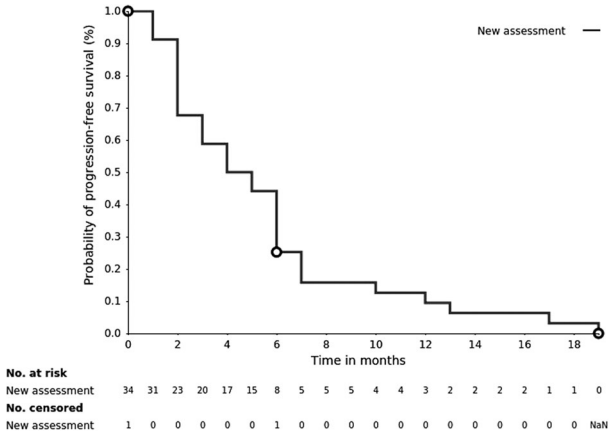



**Figure 1.** Kaplan-Meier plot of progression-free survival.

shock protein 40 fused with *PRKACA* exons 2 through 10 [2]. This results in an overexpressed chimeric protein that has intact Aurora kinase A enzymatic activity. No specific agents have been developed yet to target *PRKACA* or the gene fusion. Unfortunately, this study evaluating the Aurora kinase inhibitor ENMD-2076 in patients with FLC did not meet its primary efficacy endpoint. This is despite preclinical in vivo animal model studies demonstrating the association of AURKA with FLC [3], ENMD-2076 anti-angiogenic activity, and a clinical benefit with a partial response in one patient with FLC who relapsed after multiple prior treatments [4]. Although the *DNAJB1-PRKACA* is neither specific nor sensitive to FLC [5–7], its transcriptome characterization [3] provides critical clues that suggest potential therapeutic targets, including AURKA. However, the present study provides no rationale to further study ENMD-2076 as a single agent in FLC. The transcriptional effects of *DNAJB1-PRKACA* have nominated other targets as well [8, 9]. The study of everolimus, leuprolide, and letrozole unfortunately did not show any promise [10], despite the attempt to block the cross-communication between the estrogen receptor and PI3K/Akt/mTOR pathway [11]. Similarly, the increased expression of the breast cancer oncogene v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2 (*ErbB2*) [5] observed in FLC [3] led to the study of neratinib as monotherapy in patients with FLC (ClinicalTrials.gov: NCT01953926).

Despite the link between expression of the *DNAJB1-PRKACA* gene fusion and downstream changes of gene expression and signaling, it is not yet possible to determine whether the latter changes are the result of increased expression of *PRKACA* as a consequence of the *DNAJB1* promoter or whether there are changes in the activity of *PRKACA* [4]. It remains unclear if the chimera is sufficient for transformation or which of the changes in reported 3500 gene expression may be driving the transformation [4]. One may wonder if a simultaneous targeting approach of the presumed primary genetic driver for FLC, the chimera of *DNAJB1-PRKACA*, and the critical downstream components may be needed [12].

| Trial Information | |
|---|---|
| **Disease** | Fibrolamellar carcinoma |
| **Stage of Disease/Treatment** | Metastatic/advanced |
| **Prior Therapy** | No designated number of regimens |
| **Type of Study** | Phase II, single arm |
| **Primary Endpoint** | Overall response rate |
| **Secondary Endpoint** | 6-month progression-free survival |
| **Secondary Endpoint** | Progression-free survival |
| **Secondary Endpoint** | Time to progression |
| **Secondary Endpoint** | Overall survival |
| **Secondary Endpoint** | Toxicity |
| **Secondary Endpoint** | Correlative endpoint |
| **Investigator's Analysis** | Inactive because results did not meet primary endpoint |

| Drug Information | |
|---|---|
| **Generic/Working Name** | ENMD-2076 |
| **Company Name** | CASI Pharmaceuticals |
| **Drug Type** | Biological |
| **Drug Class** | Aurora kinase A (ARUKA) |
| **Dose** | 150 mg/day, 200 mg/day, or 250 mg/day based on body surface area (mg per flat dose) |
| **Route** | p.o. |

| Schedule of Administration | Body surface area, m[a] | Daily dose, mg |
|---|---|---|
| | <1.00 | 150 |
| | 1.00 to <1.40 | 200 |
| | ≥1.40 | 250 |

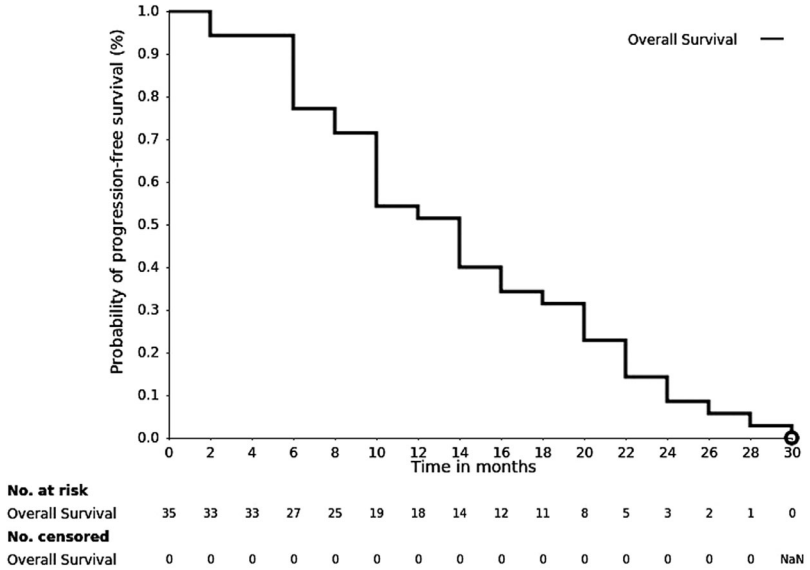
| Patient Characteristics | | |
|---|---|---|
| **Number of Patients, Male** | 16 | |
| **Number of Patients, Female** | 19 | |
| **Age** | Median (range): 25 (12–52) | |
| **Number of Prior Systemic Therapies** | Median (range): Median (Q3–Q1) is 4 (8–3) | |
| **Performance Status** | **ECOG status at baseline[a]** | ***n* (%)** |
| | 0 | 12 (36.4) |
| | 1 | 19 (57.6) |
| | 2 | 2 (6.1) |
| | **Lansky status at baseline[b]** | ***n* (%)** |
| | = 100 | 1 (50.0) |
| | = 90 | 1 (50.0) |

[a]The percentage for ECOG status at baseline is calculated using the number of patients aged 16 and older as the denominator.
[b]The percentage for Lansky status at baseline is based on the number of patients younger than 16 as the denominator.
Abbreviation: ECOG, Eastern Cooperative Oncology Group.

| Primary Assessment Method: Overall Survival | |
|---|---|
| **Number of Patients Screened** | 43 |
| **Number of Patients Enrolled** | 35 |
| **Number of Patients Evaluable for Toxicity** | 35 |
| **Number of Patients Evaluated for Efficacy** | 35 |
| **(Median) Duration Assessments OS** | 18.6, CI: 12.9–29.8 |

Kaplan-Meier Time Units, Months

| Time of scheduled assessment and/or time of event | No. progressed (or deaths) | No. censored | Percent at start of evaluation period | Kaplan-Meier % | No. at next evaluation/No. at risk |
|---|---|---|---|---|---|
| 0 | 0 | 0 | 100.00 | 100.00 | 35 |
| 2 | 2 | 0 | 100.00 | 94.29 | 33 |
| 4 | 0 | 0 | 94.29 | 94.29 | 33 |
| 6 | 6 | 0 | 94.29 | 77.14 | 27 |
| 8 | 2 | 0 | 77.14 | 71.43 | 25 |
| 10 | 6 | 0 | 71.43 | 54.29 | 19 |
| 12 | 1 | 0 | 54.29 | 51.43 | 18 |
| 14 | 4 | 0 | 51.43 | 40.00 | 14 |
| 16 | 2 | 0 | 40.00 | 34.29 | 12 |
| 18 | 1 | 0 | 34.29 | 31.43 | 11 |
| 20 | 3 | 0 | 31.43 | 22.86 | 8 |
| 22 | 3 | 0 | 22.86 | 14.29 | 5 |
| 24 | 2 | 0 | 14.29 | 8.57 | 3 |
| 26 | 1 | 0 | 8.57 | 5.71 | 2 |
| 28 | 1 | 0 | 5.71 | 2.86 | 1 |
| 30 | 1 | 0 | 2.86 | 0.00 | 0 |



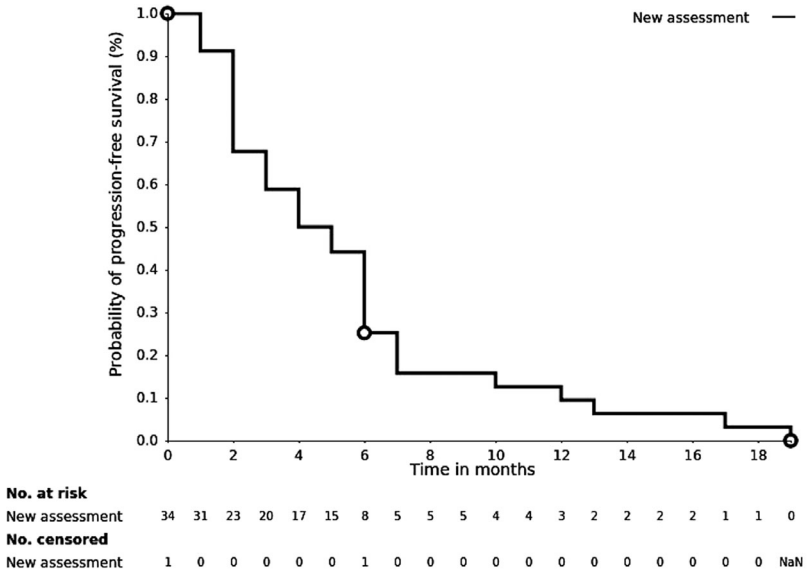

Kaplan-Meier Plot of Overall Survival (Efficacy Analysis Population)

| Primary Assessment Method: Progression-Free Survival | |
|---|---|
| **Number of Patients Screened** | 43 |
| **Number of Patients Enrolled** | 35 |
| **Number of Patients Evaluable for Toxicity** | 35 |
| **Number of Patients Evaluated for Efficacy** | 35 |
| **Evaluation Method** | RECIST 1.1 |
| **Response Assessment CR** | *n* = 0 (0%) |
| **Response Assessment PR** | *n* = 1 (3%) |
| **Response Assessment SD** | *n* = 20 (57%) |
| **Response Assessment PD** | *n* = 10 (34.3%) |
| **Response Assessment OTHER** | *n* = 2 (5.7%) |
| **(Median) Duration Assessments PFS** | 3.9 months, CI: 2.3–5.5 |
| **(Median) Duration Assessments TTP** | 5 months, CI: 0.7–5.7 |
| **(Median) Duration Assessments Response Duration** | 14.69 months |

**Kaplan-Meier Time Units, Months**

| Time of scheduled assessment and/or time of event | No. progressed (or deaths) | No. censored | Percent at start of evaluation period | Kaplan-Meier % | No. at next evaluation/No. at risk |
|---|---|---|---|---|---|
| 0 | 0 | 1 | 100.00 | 100.00 | 34 |
| 1 | 3 | 0 | 100.00 | 91.18 | 31 |
| 2 | 8 | 0 | 91.18 | 67.65 | 23 |
| 3 | 3 | 0 | 67.65 | 58.82 | 20 |
| 4 | 3 | 0 | 58.82 | 50.00 | 17 |
| 5 | 2 | 0 | 50.00 | 44.12 | 15 |
| 6 | 6 | 1 | 44.12 | 25.21 | 8 |
| 7 | 3 | 0 | 25.21 | 15.76 | 5 |
| 8 | 0 | 0 | 15.76 | 15.76 | 5 |
| 9 | 0 | 0 | 15.76 | 15.76 | 5 |
| 10 | 1 | 0 | 15.76 | 12.61 | 4 |
| 11 | 0 | 0 | 12.61 | 12.61 | 4 |

| | | | | | |
|---|---|---|---|---|---|
| 12 | 1 | 0 | 12.61 | 9.45 | 3 |
| 13 | 1 | 0 | 9.45 | 6.30 | 2 |
| 14 | 0 | 0 | 6.30 | 6.30 | 2 |
| 15 | 0 | 0 | 6.30 | 6.30 | 2 |
| 16 | 0 | 0 | 6.30 | 6.30 | 2 |
| 17 | 1 | 0 | 6.30 | 3.15 | 1 |
| 18 | 0 | 0 | 3.15 | 3.15 | 1 |
| 19 | 1 | 0 | 3.15 | 0.00 | 0 |




Kaplan-Meier Plot of Progression-Free Survival (Efficacy Analysis Population)

**Adverse Events (All Cycles)**

| Name | NC/NA | 1 | 2 | 3 | 4 | 5 | All grades |
|---|---|---|---|---|---|---|---|
| Fatigue | 23% | 66% | 11% | 0% | 0% | 0% | 77% |
| Fever | 91% | 9% | 0% | 0% | 0% | 0% | 9% |
| Chills | 94% | 6% | 0% | 0% | 0% | 0% | 6% |
| Nausea | 43% | 46% | 11% | 0% | 0% | 0% | 57% |
| Vomiting | 74% | 20% | 6% | 0% | 0% | 0% | 26% |
| Diarrhea | 35% | 37% | 11% | 17% | 0% | 0% | 65% |
| Constipation | 77% | 17% | 6% | 0% | 0% | 0% | 23% |
| Anemia | 74% | 17% | 6% | 3% | 0% | 0% | 26% |
| Neutrophil count decreased | 94% | 6% | 0% | 0% | 0% | 0% | 6% |
| Platelet count decreased | 86% | 14% | 0% | 0% | 0% | 0% | 14% |
| Blood and lymphatic system disorders—increased hemoglobin | 89% | 11% | 0% | 0% | 0% | 0% | 11% |
| INR increased | 91% | 6% | 3% | 0% | 0% | 0% | 9% |
| Activated partial thromboplastin time prolonged | 83% | 11% | 0% | 6% | 0% | 0% | 17% |
| Cough | 74% | 20% | 6% | 0% | 0% | 0% | 26% |
| Pharyngolaryngeal pain | 91% | 9% | 0% | 0% | 0% | 0% | 9% |
| Sinus disorder | 94% | 6% | 0% | 0% | 0% | 0% | 6% |
| Dyspnea | 71% | 14% | 9% | 6% | 0% | 0% | 29% |
| Weight loss | 80% | 14% | 3% | 3% | 0% | 0% | 20% |
| Gastrointestinal disorders—decreased appetite | 72% | 17% | 11% | 0% | 0% | 0% | 28% |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Dry mouth | 94% | 6% | 0% | 0% | 0% | 0% | 6% |
| Abdominal distension | 94% | 6% | 0% | 0% | 0% | 0% | 6% |
| Hypercalcemia | 91% | 6% | 3% | 0% | 0% | 0% | 9% |
| Hypomagnesemia | 71% | 23% | 6% | 0% | 0% | 0% | 29% |
| Hypertension | 58% | 11% | 20% | 11% | 0% | 0% | 42% |
| Renal and urinary disorders—hypernatremia | 91% | 9% | 0% | 0% | 0% | 0% | 9% |
| Aspartate aminotransferase increased | 31% | 43% | 17% | 9% | 0% | 0% | 69% |
| Abdominal pain | 34% | 31% | 29% | 6% | 0% | 0% | 66% |
| Alanine aminotransferase increased | 26% | 37% | 14% | 20% | 3% | 0% | 74% |
| Alkaline phosphatase increased | 57% | 26% | 14% | 3% | 0% | 0% | 43% |
| Hypoalbuminemia | 71% | 23% | 3% | 3% | 0% | 0% | 29% |
| Hypoglycemia | 91% | 9% | 0% | 0% | 0% | 0% | 9% |
| Hyperglycemia | 54% | 37% | 6% | 3% | 0% | 0% | 46% |
| Hyponatremia | 74% | 26% | 0% | 0% | 0% | 0% | 26% |
| Hyperkalemia | 83% | 14% | 3% | 0% | 0% | 0% | 17% |
| Mucositis oral | 88% | 9% | 3% | 0% | 0% | 0% | 12% |
| Dizziness | 91% | 9% | 0% | 0% | 0% | 0% | 9% |
| Palpitations | 94% | 6% | 0% | 0% | 0% | 0% | 6% |
| Dry skin | 94% | 6% | 0% | 0% | 0% | 0% | 6% |
| Rash acneiform | 86% | 14% | 0% | 0% | 0% | 0% | 14% |
| Hypocalcemia | 85% | 9% | 3% | 3% | 0% | 0% | 15% |
| Headache | 66% | 23% | 11% | 0% | 0% | 0% | 34% |
| Insomnia | 85% | 9% | 6% | 0% | 0% | 0% | 15% |
| Myalgia | 89% | 11% | 0% | 0% | 0% | 0% | 11% |
| Palmar-plantar erythrodysesthesia syndrome | 88% | 6% | 6% | 0% | 0% | 0% | 12% |
| Proteinuria | 80% | 6% | 11% | 3% | 0% | 0% | 20% |
| Blurred vision | 94% | 6% | 0% | 0% | 0% | 0% | 6% |
| White blood cell decreased | 94% | 6% | 0% | 0% | 0% | 0% | 6% |
| Rash acneiform | 94% | 6% | 0% | 0% | 0% | 0% | 6% |
| Alopecia | 97% | 3% | 0% | 0% | 0% | 0% | 3% |
| Encephalopathy | 94% | 3% | 0% | 3% | 0% | 0% | 6% |
| Fecal incontinence | 97% | 3% | 0% | 0% | 0% | 0% | 3% |
| Back pain | 88% | 3% | 6% | 3% | 0% | 0% | 12% |
| Blood bilirubin increased | 82% | 3% | 6% | 9% | 0% | 0% | 18% |
| Creatinine increased | 97% | 3% | 0% | 0% | 0% | 0% | 3% |
| Noncardiac chest pain | 94% | 6% | 0% | 0% | 0% | 0% | 6% |
| Chest pain—cardiac | 97% | 3% | 0% | 0% | 0% | 0% | 3% |
| Colitis | 97% | 3% | 0% | 0% | 0% | 0% | 3% |
| Bruising | 97% | 3% | 0% | 0% | 0% | 0% | 3% |
| Depression | 97% | 3% | 0% | 0% | 0% | 0% | 3% |
| Dyspepsia | 94% | 3% | 3% | 0% | 0% | 0% | 6% |
| Dysphasia | 97% | 3% | 0% | 0% | 0% | 0% | 3% |
| Left ventricular systolic dysfunction | 91% | 3% | 6% | 0% | 0% | 0% | 9% |
| Electrocardiogram QT corrected interval prolonged | 97% | 3% | 0% | 0% | 0% | 0% | 3% |
| Infections and infestations—enteritis | 94% | 3% | 0% | 3% | 0% | 0% | 6% |
| Epistaxis | 97% | 3% | 0% | 0% | 0% | 0% | 3% |
| Flatulence | 97% | 3% | 0% | 0% | 0% | 0% | 3% |
| Eye disorders—pain | 97% | 3% | 0% | 0% | 0% | 0% | 3% |
| Gastrointestinal disorders—reflux | 97% | 3% | 0% | 0% | 0% | 0% | 3% |
| Gastrointestinal disorders—hyperchlorhydria | 97% | 3% | 0% | 0% | 0% | 0% | 3% |
| Hyperuricemia | 97% | 3% | 0% | 0% | 0% | 0% | 3% |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Hearing impaired | 97% | 3% | 0% | 0% | 0% | 0% | 3% |
| Renal and urinary disorders—hypochloremia | 97% | 3% | 0% | 0% | 0% | 0% | 3% |
| Hypokalemia | 97% | 3% | 0% | 0% | 0% | 0% | 3% |
| Hypophosphatemia | 86% | 3% | 11% | 0% | 0% | 0% | 14% |
| Chest wall pain | 97% | 3% | 0% | 0% | 0% | 0% | 3% |
| Generalized muscle weakness | 97% | 3% | 0% | 0% | 0% | 0% | 3% |
| Pain | 94% | 6% | 0% | 0% | 0% | 0% | 6% |
| Edema limbs | 97% | 3% | 0% | 0% | 0% | 0% | 3% |
| Neck pain | 97% | 3% | 0% | 0% | 0% | 0% | 3% |
| Infections and infestations—candidiasis | 97% | 3% | 0% | 0% | 0% | 0% | 3% |
| Peripheral sensory neuropathy | 97% | 3% | 0% | 0% | 0% | 0% | 3% |
| Pelvic pain | 94% | 3% | 3% | 0% | 0% | 0% | 6% |
| Gastrointestinal disorders—polydipsia | 97% | 3% | 0% | 0% | 0% | 0% | 3% |
| Blood and lymphatic system disorders—polycythemia | 97% | 3% | 0% | 0% | 0% | 0% | 3% |
| Rash acneiform | 83% | 17% | 0% | 0% | 0% | 0% | 17% |
| Respiratory, thoracic, and mediastinal disorders—rhinorrhea | 97% | 3% | 0% | 0% | 0% | 0% | 3% |
| Insomnia | 97% | 3% | 0% | 0% | 0% | 0% | 3% |
| Tinnitus | 97% | 3% | 0% | 0% | 0% | 0% | 3% |
| Reproductive system and breast disorders—wheezing | 97% | 3% | 0% | 0% | 0% | 0% | 3% |
| Infections and infestations—bacteremia | 97% | 0% | 0% | 0% | 3% | 0% | 3% |
| Amnesia | 97% | 0% | 3% | 0% | 0% | 0% | 3% |
| Respiratory failure | 97% | 0% | 0% | 0% | 3% | 0% | 3% |
| Colitis | 91% | 0% | 0% | 9% | 0% | 0% | 9% |
| Infections and infestations—*Clostridium difficile* | 97% | 0% | 3% | 0% | 0% | 0% | 3% |
| Blood and lymphatic system disorders—deep vein thrombosis | 97% | 0% | 3% | 0% | 0% | 0% | 3% |
| Dehydration | 94% | 0% | 3% | 3% | 0% | 0% | 6% |
| Thromboembolic event | 94% | 0% | 0% | 6% | 0% | 0% | 6% |
| Cardiac disorders—diastolic hypertension | 97% | 0% | 3% | 0% | 0% | 0% | 3% |
| Gastrointestinal disorders—hematemesis | 97% | 0% | 3% | 0% | 0% | 0% | 3% |
| Hypotension | 97% | 0% | 0% | 3% | 0% | 0% | 3% |
| Hypothyroidism | 94% | 0% | 6% | 0% | 0% | 0% | 6% |
| Hypoxia | 97% | 0% | 0% | 0% | 3% | 0% | 3% |
| Infections and infestations—skin | 97% | 0% | 0% | 3% | 0% | 0% | 3% |
| Irritability | 97% | 0% | 3% | 0% | 0% | 0% | 3% |
| Lymphocyte count decreased | 94% | 0% | 0% | 6% | 0% | 0% | 6% |
| Confusion | 97% | 0% | 3% | 0% | 0% | 0% | 3% |
| Bone pain | 97% | 0% | 3% | 0% | 0% | 0% | 3% |
| Photophobia | 97% | 0% | 3% | 0% | 0% | 0% | 3% |
| General disorders and administration site conditions—night sweats | 97% | 0% | 3% | 0% | 0% | 0% | 3% |
| Pleural effusion | 97% | 0% | 3% | 0% | 0% | 0% | 3% |
| Pleuritic pain | 97% | 0% | 3% | 0% | 0% | 0% | 3% |
| Fracture | 97% | 0% | 3% | 0% | 0% | 0% | 3% |
| Seizure | 97% | 0% | 0% | 3% | 0% | 0% | 3% |
| Upper respiratory infection | 97% | 0% | 3% | 0% | 0% | 0% | 3% |
| Sepsis | 97% | 0% | 0% | 0% | 3% | 0% | 3% |
| Sinus tachycardia | 91% | 0% | 9% | 0% | 0% | 0% | 9% |
| Rhinitis infective | 97% | 0% | 3% | 0% | 0% | 0% | 3% |
| Urinary tract infection | 97% | 0% | 3% | 0% | 0% | 0% | 3% |

Abbreviation: NC/NA, no change from baseline/no adverse event.

| Serious Adverse Events | | |
|---|---|---|
| **Name** | **Grade** | **Attribution** |
| Sepsis | 4 | Unlikely |
| Liver failure | 4 | Possible |
| Respiratory failure | 4 | Unlikely |
| Seizure | 3 | Possible |

| Assessment, Analysis, and Discussion | |
|---|---|
| **Completion** | Study completed |
| **Investigator's Assessment** | Inactive because results did not meet primary endpoint |

Fibrolamellar carcinoma (FLC) was first described by Edmondson in 1956 [13]. It is a distinctly uncommon primary liver neoplasm and very rare cancer of adolescents and young adults [2]. It represents 0.6%–8.6% of all hepatocellular carcinomas based on the 1986–1999 Surveillance, Epidemiology, and End Results data and various international series [14]. FLC is characterized pathologically with large polygonal cells with abundant eosinophilic cytoplasm and large nucleoli. The term fibrolamellar is related to the presence of thick fibrous collagen bands surrounding the cancer cells. Cytoplasmic pale bodies and copper deposits may be present. On immunohistochemistry, the presumed correlated to liver and/or neuroendocrine primary, α-fetoprotein, synaptophysin, and chromogranin, are typically absent. In contrast, immunoreactivity for HepPar-1, polyclonal carcinoembryonic antigen (pCEA), cytokeratin 7, and epithelial membrane antigen is present in nearly all FLC tumors, suggesting that this disease entity may be a hepatobiliary hybrid [15]. Data suggest a slight female preponderance [14]. The relatively high prevalence of this disease among whites is noteworthy and may represent referral bias, with a possible socioeconomic undercurrent. Reports of long-term survival with resection and/or transplantation helped promote a perception of FLC as being an indolent disease. In the referenced cohort of 95 patients with FLC collected from three institutions (Memorial Sloan Kettering Cancer Center, the University of California San Francisco, and Johns Hopkins Hospital) from 1986 to 2011, median overall survival for the entire cohort was 6.7 years, with a median follow-up time for living patients of 3.4 years, showing high recurrence rates after surgery [14]. Factors significantly associated with poor survival were female sex, advanced stage, lymph node metastases, macrovascular invasion, and unresectable disease.

It appears that the cancer is driven by a fusion gene, *DNAJB1-PRKACA*, comprising the first exon of *DNAJB1*, the heat-shock protein 40 fused with *PRKACA* exons 2 through 10 [2]. No specific agents have been developed yet to target *PRKACA* or the gene fusion.

Unfortunately, this study evaluating the Aurora kinase A (AURKA) inhibitor ENMD-2076 in patients with FLC did not meet its primary efficacy endpoint. This is despite preclinical in vivo animal model studies demonstrating the association of AURKA with FLC [3], ENMD-2076 antiangiogenic activity, and a clinical benefit with a partial response in one patient with FLC who relapsed after multiple prior treatments [4]. Although the *DNAJB1-PRKACA* is neither specific nor sensitive to FLC [5–7], its transcriptome characterization [3] provides critical clues that suggest potential therapeutic targets, including AURKA. However, the present study provides no rationale to further study ENMD-2076 as a single agent in FLC, but it does seem to suggest a combination multitargeted therapeutic approach rather than a single-agent approach. The transcriptional effects of *DNAJB1-PRKACA* have nominated other targets as well. We started our efforts based on the postulation that FLC has a neuroendocrine origin [8, 9]. Unfortunately, the study of everolimus, leuprolide, and letrozole did not show any promise [10], despite the attempt to block the cross-communication between the estrogen receptor and PI3K/Akt/mTOR pathway [11]. Similarly, the increased expression of the breast cancer oncogene v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2 (*ErbB2*) [5] observed in FLC [3] led to the study of neratinib as monotherapy in patients with FLC (ClinicalTrials.gov: NCT01953926). The present work using an Aurora kinase A inhibitor also derived from study of the transcriptional effects of DNAJB1-PRKACA.

This effort was also based on nonreported preclinical study of three different human hepatocellular carcinoma cell lines (SMMC-7721, QGY-7703, and HepG 2) with tumor xenograft models in nude mice. These cell lines were subject to ENMD-2076 treatment alone or in combination with chemotherapy agents, including doxorubicin or fluorouracil. The following clinical studies were encouraging with a clinical benefit observed with one unconfirmed partial response in a patient with FLC as mentioned above. The patient relapsed after multiple treatments including transarterial chemo embolization (TACE)/doxorubicin, TACE/cisplatin, liver transplantation, and sorafenib. The patient was on ENMD-2076 for eighteen 4-week cycles while maintaining stable disease for 17 months [4].

Despite the link between expression of the gene fusion and changes of gene expression and signaling, it is, as yet, not possible to determine whether the changes are the result of increased expression of the PRKACA as a consequence of the DNAJB1 promoter, or changes of activity of PRKACA [4]. More than 3,500 genetic expression changes have been noted in FLC [4]. It remains unclear if these widespread gene expression changes could be accounted for by AURKA effects on transcription factors, and if the chimera is sufficient for transformation or which of the changes in gene expression are driving the transformation. Thus, a simultaneous targeting approach of the presumed primary genetic driver for FLC, the chimera of DNAJB1-PRKACA, and the critical downstream components may be needed [12].

## Disclosures

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